REMARKS

It is respectfully requested that the application be reconsidered in view of the above amendments and the following remarks and that all of the claims now present in this application be allowed.

Interview

At the outset, the undersigned thanks Examiners Yaen and Brumback for the courtesies extended to himself, Dawn Gardner, Dr. Anthony Bolton and R. Hirons during the personal interview conducted for this application. The Interview Summary provided by the Examiner accurately summarizes Applicants' position set forth during the interview. Applicants' position is further elaborated upon below.

Specification Amendments:

Applicants submit that the amendments made to the specification are requested in order to correct misspellings and typographical errors. No new matter has been added by the Amendments. Entry of these amendments is respectfully requested.

Claim Amendments:

The amendments made herein are requested solely to expedite the prosecution of what is to be believed to be allowable subject matter. Applicants specifically reserve the right to file one or more continuation/divisional applications to present claims directed to the canceled subject matter.

Claims 2, 11 and 15 have been canceled without prejudice or disclaimer to Applicants filing one or more continuation or divisional applications directed to the subject matter therein.

Claims 1 has been replaced by Claim 16 and embodies the recitation of canceled Claims 1, 11 and 15. Claims 3-10 and 12-14 have been replaced by Claims 17-28, which

are now in appropriate method claim format and depend either directly or indirectly on Claim 16. No new matter has been added by the Amendments. Entry of these amendments is respectfully requested.

Objection under 37 C.F.R. § 1.75

The Examiner's objection of Claim 1 under 37 C.F.R. § 1.75 as being a substantial duplicate of Claim 15 is respectfully traversed. Upon entry of Applicants' request to cancel Claim 15, this objection will be moot. Accordingly, reconsideration and withdrawal of this objection is respectfully requested.

Rejections under 35 U.S.C. § 112, Second Paragraph

The Examiner's rejection of Claims 1-8 and 12-15 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to point out and distinctly claim the subject matter which applicants regard as the invention, is respectfully traversed. With regard to Claim 15, upon entry of Applicants' request to cancel Claim15, this rejection will be moot. With respect to the remaining claims, each specific rejection is addressed below.

(a) The Examiner's rejection of Claims 1-7 and 12-15, as allegedly unclear in the use of the phrase "apoptotic body and/or apoptotic cell" is respectfully traversed. Applicants understand that the confusion of the language lies in the redundancy of the recitation of both apoptotic cells and apoptotic bodies and that these terms were commonly defined. Therefore, Claims 1-7 and 12-14 have been replaced by Claims 17-28 and the phrase "and/or apoptotic cell" has been removed in the newly presented claims to delete any redundancy. Applicants submit that this obviates the rejection. Reconsideration and withdrawal of this rejection are respectfully requested.

(b) The Examiner's rejection of Claims 1-14 as being unclear for failing to set forth any steps involved in the method/process, is respectfully traversed. Claims 1-10 and 12-14 have been replaced with Claims 16-28 to properly reflect that the claimed method is directed to administration of an effective amount of apoptotic bodies to a mammalian patient suffering from various medical disorders resulting from endothelial dysfunction. Reconsideration and withdrawal of this rejection are respectfully requested.

(c) The Examiner's rejection of Claims 1-14 under 35 U.S.C. § 101 as allegedly claiming recitation of a use without setting forth any steps involved in the process is respectfully traversed. Claims 1-10 and 12-14 have been replaced with new claims 17-28 which properly reflect the method of the disclosed invention, rendering this rejection moot. In light of the claim amendments, reconsideration and withdrawal of this rejection is respectfully requested.

Double Patenting

The Examiner's provisional rejection of Claims 3-14 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 3-14 of copending Application No. 09/866,488 (hereinafter the '488 Application), is respectfully traversed. Applicants note that Claims 3-14 are now embodied in the newly presented Claims 17-28.

Obviousness-type double patenting requires rejection of an application claim when the claimed subject matter is not patently distinct from the subject matter claimed. Any rejection based on obviousness-type double patenting should make clear (1) the difference between the inventions defined by the conflicting claims and (2) the reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim is an obvious variation of the invention defined in a claim in the patent. *See* MPEP §804.

The Examiner contends that although the conflicting claims are not identical, they are not patently distinct from Claims 3-14 of the '488 Application because they both recite the

use of apoptotic bodies and/or apoptotic cells in preparative steps in the treatment of disease types and in the dosage of the medicament. Initially, Applicants submit that Claims 17-28 in present application and Claims 3-14 in the '488 Application are all dependent claims and dependent claims include every limitation of the claim from which it depends. *See* MPEP §608.01(n). Thus the dependent claims are directed to the combination including everything recited in the independent claim and what is recited in the dependent claim. Therefore, although the dependent claims in both applications are directed to use of apoptotic bodies, the claims must be read in light of the claims from which they depend. In the present application, the claims depend directly or indirectly from Claim 16, which are now directed to a method for treatment or prophylaxis for medical disorders resulting from endothelial dysfunction, while in the '488 Application, Claims 1 and 2 are directed to treatment of T-cell mediated disorders or inflammatory disorders. In point of fact, there is no rejection of the independent claims over each other in the copending applications. Accordingly, the rejection is improper because the claims are patently distinct as they are directed to treating different disorders.

Reconsideration and withdrawal of this rejection is respectfully requested.

Claim Rejections under 35 U.S.C. § 102(b)

Claims 1, 2 and 15 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Henry, et al. (*Pathobio.*, 67(5-6): 306-310 (1999)) (hereinafter the Henry Reference). With regard to Claims 2 and 15, upon entry of Applicants' request to cancel Claims 2 and 15, this rejection will be moot. With respect to Claim 1, which is now embodied in Claim 16, the rejection is traversed.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *See, Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ.2d 1051, 1053 (Fed. Cir. 1987). The Examiner contends that the Henry Reference teaches the isolation and successful administration of the apoptotic bodies to a mammalian patient.

However, the Henry Reference is directed to using apoptotic bodies for treatment of cancer. *See, for example*, the Henry Reference, Abstract.

The presently claimed invention, as now amended, is directed to a method of treatment or prophylaxis for medical disorders resulting from endothelial dysfunction, which disorders include atherosclerosis, peripheral vascular disease, congestive heart failure, stroke, myocardial infarction, angina, hypertension, Raynaud's disease, cardiac syndrome X, migraine, ischemic damage, inflammatory bowel disease and graft versus host disease. The Henry Reference does not disclose any of the named disorders in the presently claimed invention. Accordingly, reconsideration and withdrawal of this rejection is requested.

Claim Rejections under 35 U.S.C. § 103

The Examiner's rejection of Claims 3-5 and 12-14 under 35 U.S.C. § 103(a) as unpatentable over the Henry Reference is respectfully traversed. As previously mentioned Claims 3-5 and 12-14 are now embodied in Claims 17-28.

To properly issue a rejection under 35 U.S.C. § 103(a), the Patent Office bears the initial burden to establish a *prima facie* case of obviousness by meeting three criteria. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings to arrive at the claimed invention. *In re Vaeck*, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991). Second, there must be a reasonable expectation of success. *Id.* Finally, the prior art reference or the combination of references must teach or suggest all the claim limitations. *In re Royka*, 180 U.S.P.Q. 580 (C.C.P.A. 1974).

Applicants submit that citation of the Henry reference is in error because there is no suggestion or motivation to arrive at the claimed invention. In fact, the Henry Reference does not teach or suggest all the claim limitations.

As previously stated, the Henry Reference discloses the use and administration of apoptotic bodies and/or apoptotic cells in the treatment of the cancer. However, as now claimed, the present invention is directed toward treatment of medical disorders resulting from endothelial dysfunction, which disorders include atherosclerosis, peripheral vascular disease, congestive heart failure, stroke, myocardial infarction, angina, hypertension, Raynaud's disease, cardiac syndrome X, migraine, ischemic damage, inflammatory bowel disease and graft versus host disease. There is no teaching or suggestion of treating any of the named diseases in the Henry Reference. Further, given the distinct pathogenesis of the claimed disorders, a skilled artisan would not be motivated to use a cancer treatment to treat any of the specifically named disorders.

Still further, while the Office Action admits that there is no disclosure of precise percentages of cellular content to be administered and/or specific dosages of cells to be administered, it alleges that it would have been obvious to one of ordinary skill at the time the invention was made to use the percentage of cells and the number of cells disclosed in the instant application. However, in view of the newly presented claims, the application and the reference are directed at treating different diseases, thus rendering the rejection moot.

Accordingly, in light of the embodiment of former Claims 1, 11, and 15, in the newly presented Claim 16, the disclosure of the Henry Reference does not render the claimed invention obvious. Therefore, Applicants respectfully request that this rejection be withdrawn.

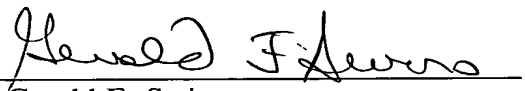
Conclusions:

For the reasons set forth above, Applicants submit that the claims of this application are patentable. Reconsideration and withdrawal of the Examiner's rejections are hereby requested. Allowance of the claims remaining in this application is earnestly solicited.

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is requested to call the undersigned at (650) 622-2324.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: 

Gerald F. Swiss
Registration No. 30,113

P.O. Box 1404
Alexandria, Virginia 22313-1404
(650) 622-2300

Date: August 26, 2002

APPENDIX I

MARKED UP VERSION SHOWING CHANGES MADE TO THE AMENDED SPECIFICATION

Amend the paragraph bridging pages 1 and 2 to read as follows:

--Two mechanisms of cell death in the body are recognized, necrosis and apoptosis. Apoptosis is the process of programmed cell death, described by Kerr et al in 1992 [[](Kerr JFR, Wyllie AH, Currie AR (1992). "Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. *"British Journal of Cancer* **26:** 239-257")[]], by which steady-state levels of the various organ systems and tissues in the body are maintained as continuous cell division and differentiation takes place. Cells undergoing apoptosis often exhibit distinctive morphological changes such as a pronounced decrease in cell volume, modification of the cytoskeletons resulting in pronounced membrane blebbing, a condensation of the chromatin, and degradation of the DNA into oligonucleosomal fragments. Following these morphological changes, an apoptotic cell may break up into a number of small fragments known as apoptotic bodies, comprising membrane-bound bodies containing intact organelles, chromatin, etc. Apoptotic bodies are normally rapidly removed from the body by phagocytosis by macrophages, dendritic cells and other antigen-presenting cells, before they can become lysed and release their potentially pro-inflammatory intracellular contents.--

Amend the paragraph at page 3, lines 3-16, to read as follows:

--Many cells undergoing apoptosis can be identified by a characteristic 'laddering' of DNA seen on agarose gel electrophoresis, resulting from cleavage of DNA into a series of fragments. These changes occur a few hours before death of the cell as defined by the ability of a cell to exclude vital dyes. The appearance of DNA laddering on agarose gel electrophoresis following extraction of DNA from cells is one [recognised] recognized method of identification of apoptosis in cells [[](Loo, D.T. and Rillema, J.R. (1998) "Measurement of Cell Death," *Methods in Cell Biology* **57**: 251-264)[]], although it is not always sensitive enough to detect apoptosis. *In situ* [labelling] **labeling** of nuclear DNA fragmentation, for example, using commercially available terminal dUTP nick end [labelling] **labeling** (TUNEL) assays, [are] **is** an alternative and more reproducible measure for the determination of fragmented DNA in apoptotic cells and cells undergoing apoptosis [[](Gavrieli Y, Sherman Y, Ben-Sasson SA (1992) "Identification of programmed cell death in situ via specific labelling of nuclear DNA fragmentation," *Journal of Cell Biology* **119:** 493-501)[]].--

Amend the paragraph at page 3, lines 17-26, to read as follows:

--During apoptosis, phosphatidylserine becomes exposed externally on the cell membrane [[](Fadok VA, Voelker DR, Campbell PA, Cohen JJ, Bratton DL, Henson PM (1992), "Exposure of phosphatidylserine on the surface of apoptotic lymphocytes triggers specific recognition and removal by macrophages". *Journal of Immunology* **148:** 2207-2216)[]] and this exposed phosphatidylserine binds to specific receptors to mediate the uptake and clearance of apoptotic cells in mammals [[](Fadok VA, Bratton DL, Rose DM, Pearson A, Ezekewitz RAB, Henson PM (2000), "A receptor for phosphatidylserine-specific clearance of apoptotic cells", *Nature* **405:** 85-90)[]]. The surface expression of phosphatidylserine on cells is another [recognised] **recognized** method of identification of apoptotic cells.--

Amend the paragraph at page 4, lines 1-9, to read as follows:

--Changes in mitochondrial integrity are intimately associated with apoptosis, resulting in alterations in mitochondrial membrane permeability and the release of cytochrome-c from the mitochondria into the cell cytoplasm [[](Susin, S.A., Lorenzo, H.K., Zamzami, N., Marzo, I, Brenner, C., Larochette, N., Prevost, M.C., Alzari, P.M. and Kroemer, G. (1999) "Mitochondrial Release of Caspase-2 and -9 during the Apoptotic Process", *Journal of Experimental Medicine,* **189**: 381 - 394)[]]. Measurement of changes in mitochondrial membrane potential, reflecting changes in mitochondrial membrane permeability, is another [recognised] **recognized** method of identification of apoptotic cells.--

Amend the paragraph at page 6, lines 3-10, to read as follows:

--Normally, the endothelium maintains vascular homeostasis by responding to physiological stimuli, for example, changes in blood flow, oxygen tension etc., by adaptive alteration of function. Dysfunctional endothelium has an impaired response to such physiological stimuli, and can ultimately lead to medical disorders. A number of subsets of endothelial dysfunction have been recognized, including Endothelial Activation, and Endothelial-mediated Vasodilatory Dysfunction [[](see De Caterina (2000). "Endothelial dysfunctions: common denominators in vascular disease". Current Opinions in Lipidology 11:9-23)[]].--

Amend the paragraph bridging pages 6 and 7 to read as follows:

--Endothelial-mediated Vasodilatory Dysfunction is characterized by a reduction or loss of endothelium-dependent vasodilation and involves "decreased nitric oxide bioavailability" (decreased production, increased destruction and/or decreased sensitivity to nitric oxide). [[](De Caterina (2000), cited above)[]]. Nitric oxide induces vasodilation by relaxing the smooth muscle cells of the blood vessel wall. Endothelial-mediated Vasodilatory Dysfunction can be measured as a reduction in vasodilation in response to

acetylcholine, or as a reduced vasodilatory response following occlusion of arterial blood flow (reactive hyperaemia) for example using a sphygmomanometer cuff. As well as leading to a reduction in vasodilation, decreased endothelial nitric oxide bioavailability can also result in an increase in the production of vaso-constriction and hypertension. Platelet aggregation is inhibited by nitric oxide, hence a decrease in nitric oxide bioavailability can lead to an increase in platelet aggregation and consequent thrombosis. These are just a few examples of how decreased nitric oxide bioavailability resulting from Endothelial-mediated Vasodilatory Dysfunction can have pathological consequences.--

Amend the paragraph bridging pages 7 and 8 to read as follows:

--"Apoptotic cells" and "apoptotic bodies," as the terms are used herein, means cells and cell bodies which exhibit one or more of the following apoptosis-characterizing features: surface exposure of phosphatidylserine, as detected by standard, accepted methods of detection such as Annexin V staining; alterations in mitochondrial membrane permeability measured by standard, accepted methods (e.g. Salvioli, S., Ardizzoni, A., Franceschi, C. Cossarizza, A. (1997) "JC-1, but not DiOC6(3) or Rhodamine 123, is a Reliable Fluorescent Probe to assess Delta Psi Changes in Intact Cells: Implications for Studies on Mitochondrial Functionality during Apoptosis," *FEBS Letters* **411:** 77-82)[]]; evidence of DNA fragmentation such as the appearance of DNA laddering on agarose gel electrophoresis following extraction of DNA from the cells [[](Teiger, E., Dam, T.V., Richard, L., Wisnewsky, C., Tea, B.S., Gaboury, L., Tremblay, J., Schwartz, K. and Hamet, P. (1996) "Apoptosis in Pressure Overload-induced Heart Hypertrophy in the Rat," *Journal of Clinical Investigation* **97**; 2891-2897)[]], or by *in situ* labeling (see Gavrieli et al., 1992, referenced above).--

Amend the paragraph at page 9, lines 5-10, to read as follows:

--A variety of methods of inducing apoptosis in mammalian cells, so as to create apoptotic cells and/or apoptotic bodies, are known in the art and essentially any of these can be adopted in preparing apoptotic bodies for use in the present invention. One such method is the subjection of the cells to ionizing radiation (γ-rays, x-rays, etc.) and/or [non ionizing] non-ionizing electromagnetic radiation including ultraviolet light. Apoptosis can be induced by subjecting cells to ultrasound.--

Amend the paragraph bridging pages 9 and 10 to read as follows:

--Another method is the treatment of the cells with drugs such as non-specific protein kinase inhibitors as exemplified by staurosporine (see Bombeli, Karsan, Tait and Hirlan, (1997) "Apoptotic Vascular Endothelial Cells Become Procoagulant", Blood, Vol. 89:2429-2442). Also, certain chemotherapeutic agents used for the treatment of malignant tumours induce apoptosis, for example, adriamycin, as can statin drugs (3-hydroxy-3methylglutaryl coenzyme A reductase inhibitors) [[](Guijarro C, Blanco-Colio LM,

Ortego M, Alonso C, Ortiz A, Plaza JJ, Diaz C, Hernandez G, Edigo J (1998), "3-hydroxy-3methylglutaryl coenzyme A reductase and isoprenylation inhibitors induce apoptosis of vascular smooth muscle in culture," *Circulation Research* **83:** 490-500)[]] and colcicine [[](Suzuki Y (1998)", "Cell death, phagocytosis and neurogenesis in mouse olfactory epithelium and vomeronasal organ after colcicine treatment," *Annals of the New York Academy of Sciences* **855:** 252-254)[]]. The use of ligands for death receptors on cells, such as Fas-ligand, will be apparent for inducing apoptosis from the discussion of apoptosis above. A further method is the application of oxidative stress to cells extracorporeally (see for example Buttke and Sandstrom (1994) "Oxidative Stress as a Mediator of Apoptosis," Immunology Today, Vol. 15:7-10). This can be achieved by treating the cells, in suspension, with chemical oxidizing agents such as hydrogen peroxide, other peroxides and hydroperoxides, ozone, permanganates, periodates, and the like. Biologically acceptable oxidizing agents are preferably used, so as to reduce potential problems associated with residues and contaminations of the apoptotic cells and/or apoptotic bodies so formed.--

Amend the paragraph at page 10, lines 16-27, to read as follows:

--In preparing the apoptotic cells and/or apoptotic bodies, care should be taken not to apply excessive levels of oxidative stress, radiation, drug treatment, etc., since otherwise there is a significant risk of causing necrosis of at least some of the cells under treatment. Necrosis causes cell membrane rupture and the release of cellular contents**[,]** often with biologically harmful results, particularly inflammatory events, so that the presence of necrotic cells and their components along with the apoptotic bodies is best avoided. Appropriate levels of treatment of the cells to create apoptotic bodies for use in the present invention depend to some extent on the nature of the chosen cells and cellular composition, and the type of treatment chosen to induce apoptosis. Such appropriate levels are readily determinable by those skilled in the art, having regard to the available scientific literature on the subject including the above-reference articles.--

APPENDIX II

CONFORMED CLAIMS

16. (New) A method for treatment and/or prophylaxis in mammalian patients with medical disorders resulting from or involving endothelial dysfunction, wherein the disorder is selected from the group consisting of atherosclerosis, peripheral vascular disease, congestive heart failure, stroke, myocardial infarction, angina, hypertension, Raynaud's disease, cardiac syndrome X, migraine, ischemic damage, inflammatory bowel disease and graft versus host disease, which method comprises administration to the patient of an effective amount of apoptotic bodies.

17. (New) The method of Claim 16 wherein the apoptotic bodies are in a liquid suspension along with viable cells.

18. (New) The method of Claim 17 wherein the apoptotic bodies comprise from 10% to 90% of the cellular portion of the suspension.

19. (New) The method of Claim 18 wherein the apoptotic bodies comprise from 30% to 70% of the cellular portion of the suspension.

20. (New) The method of Claim 18 wherein the apoptotic bodies are derived from extracorporeal treatment of blood cells compatible with those of the mammalian patient.

21. (New) The method of Claim 16 wherein the apoptotic bodies are derived from established cultured cell lines.

22. (New) The method of Claim 20 wherein the blood cells are white blood cells of blood compatible with that of the mammalian patient.

23. (New) The method of Claim 22 wherein the blood cells are the patient's own white blood cells.

24. (New) The method of Claim 23 wherein the blood cells are the patient's own T lymphocytes.

25. (New) The method of Claim 16 wherein the effective amount of apoptotic bodies comprises from 10,000 to 10,000,000 apoptotic bodies per kilogram body weight of the patient, administered as a dosage.

26. (New) The method of Claim 25 wherein the dosage contains from 500,000 to 5,000,000 apoptotic bodies per kilogram body weight of the patient.

27. (New) The method of Claim 25 wherein the dosage contains from 1,500,000 to 4,000,000 apoptotic bodies per kilogram body weight of the patient.

28. (New) The method of Claim 25, wherein the mammalian patient is a human.